I,

or a pharmaceutically acceptable salt thereof, wherein:

R_1 is aryl or heteroaryl;

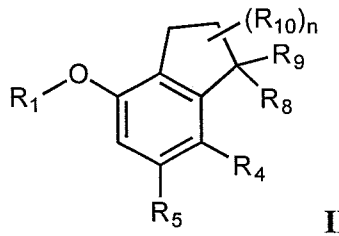
R_2 is nitro, carboxaldehyde, carboxylic acid, ester, amido, cyano, halo, sulfonyl, alkyl or heteroalkyl;

R_3 is hydrogen, halo, cyano, alkyl, heteroalkyl, alkenyl, alkynyl, alkylamino, carboxaldehyde, carboxylic acid, oxime, ester, amido or acyl, or R_2/R_3 and atoms they are attached to form a 5- or 6- membered carbocycle with at least one sp^3 hybridized carbon;

R_4 is nitro, halo, cyano, alkyl, sulfinyl, sulfonamide, sulfonyl or sulfoximinyl; and

R_5 is hydrogen, halo or alkyl.

[006a] In another aspect, the present disclosure provides a compound represented by Formula III:



III,

or a pharmaceutically acceptable salt thereof, wherein:

n is 1, 2, 3 or 4;

R_1 is aryl or heteroaryl;

R_4 is cyano, fluoroalkyl, sulfinyl, sulfonamide, sulfonyl or sulfoximinyl;

R_5 is hydrogen, halo or alkyl;

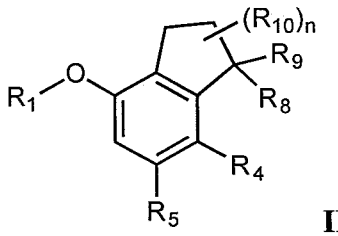
R_8 is hydrogen, hydroxy, alkylamino, alkoxy or amino;

R_9 is hydrogen, alkyl, alkenyl or alkynyl; or R_8 and R_9 in combination form oxo or oxime; and

each of R_{10} is independently selected from the group consisting of fluoro, chloro, hydroxy, and alkyl; or two R_{10} and the carbon atom(s) they are attached to form a 3- to 8-membered cycloalkyl or heterocycloalkyl.

[006b] In another aspect, the present disclosure provides a pharmaceutical composition comprising a compound as described herein, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

[006c] In another aspect, the present disclosure provides a use of a therapeutically effective amount of a compound of Formula III:



III,

or a pharmaceutically acceptable salt thereof, wherein:

n is 1, 2, 3 or 4;

R_1 is aryl or heteroaryl;

R_4 is nitro, halo, cyano, alkyl, sulfinyl, sulfonamide, sulfonyl or sulfoximinyl;

R_5 is hydrogen, halo or alkyl;

R_8 is hydrogen, hydroxy, alkylamino, alkoxy or amino;

R_9 is hydrogen, alkyl, alkenyl or alkynyl; or R_8 and R_9 in combination form oxo or oxime; and

each of R_{10} is independently selected from the group consisting of hydrogen, fluoro, chloro, hydroxy, and alkyl; or two R_{10} and the carbon atom(s) they are attached to form a 3- to 8-membered cycloalkyl or heterocycloalkyl,

in the manufacture of a medicament for treating renal cell carcinoma (RCC) in a subject.

[007] In another aspect, the present disclosure provides a pharmaceutical composition comprising a compound described herein and a pharmaceutically acceptable carrier or excipient. The compound may exist in an amorphous form, a crystalline form, or as a salt, solvate or hydrate.

[008] In another aspect, the present disclosure provides a method of treating renal cell carcinoma by administrating a therapeutically effective amount of a compound described herein or a pharmaceutical composition thereof to a subject in need of such treatment. In some embodiments, the subject is a human.

[009] In another aspect, the present disclosure provides a method of inhibiting the activities of HIF-2α in a cell, comprising contacting the cell with an effective amount of a compound described herein.

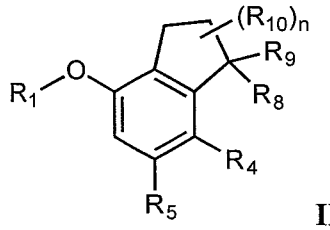
[010] In another aspect, the present disclosure provides a kit comprising a pharmaceutical composition comprising a compound described herein and a pharmaceutically acceptable carrier or excipient and an instruction for using the composition to treat a subject suffering from cancer. In some embodiments, the cancer is renal cell carcinoma.

Brief Description of Figures

[011] **Figure 1** shows treatment of renal cell carcinoma 786-O xenograft bearing mice at 0 mg/kg (denoted as "Veh"), 10 mg/kg, 30 mg/kg, and 100 mg/kg of **Compound 15** three times each at 12 hour intervals. **Figure 1** shows that **Compound 15** treatment of renal cell carcinoma 786-O xenograft bearing mice reduced the mRNA levels of HIF-2α and HIF-2α-regulated genes (PAI-1, CCND1, VEGFA, and GLUT1) in tumor. **Compound 15** had no

What is claimed is:

1. A compound represented by Formula III:



III,

or a pharmaceutically acceptable salt thereof, wherein:

n is 1, 2, 3 or 4;

R_1 is aryl or heteroaryl;

R_4 is cyano, fluoroalkyl, sulfinyl, sulfonamide, sulfonyl or sulfoximinyl;

R_5 is hydrogen, halo or alkyl;

R_8 is hydrogen, hydroxy, alkylamino, alkoxy or amino;

R_9 is hydrogen, alkyl, alkenyl or alkynyl; or R_8 and R_9 in combination form oxo or oxime; and

each of R_{10} is independently selected from the group consisting of fluoro, chloro, hydroxy, and alkyl; or two R_{10} and the carbon atom(s) they are attached to form a 3- to 8-membered cycloalkyl or heterocycloalkyl.

2. The compound of claim 1, wherein R_1 is phenyl or pyridyl, wherein said phenyl or pyridyl is substituted with at least one substituent selected from the group consisting of halo, C1-C4 alkyl, C1-C4 alkoxy, and cyano.

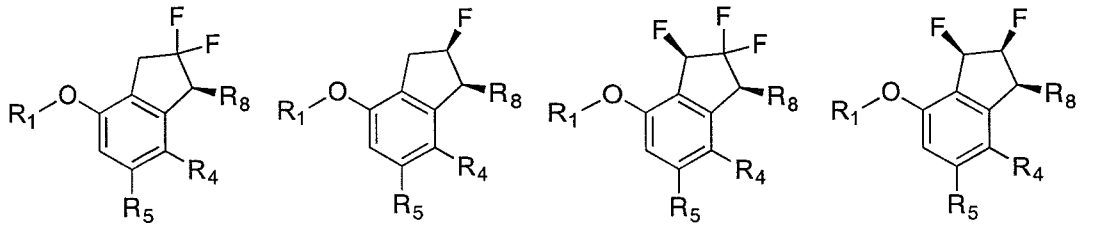
3. The compound of claim 1, wherein R_8 is hydroxy or amino.

4. The compound of claim 1, wherein R_9 is hydrogen.

5. The compound of claim 1, wherein R_{10} is fluoro and n is 1, 2 or 3.

6. The compound of claim 1, wherein R_4 is cyano, fluoroalkyl, sulfinyl, sulfonamide, sulfonyl or sulfoximinyl; R_5 is hydrogen; R_8 is hydroxy or amino; and R_9 is hydrogen.

7. The compound of claim 1, represented by Formula Va, Vb, Vc, or Vd:



or a pharmaceutically acceptable salt thereof, wherein:

R_1 is aryl or heteroaryl;

R_4 is cyano, fluoroalkyl, sulfonamide, sulfinyl, sulfonyl or sulfoximinyl;

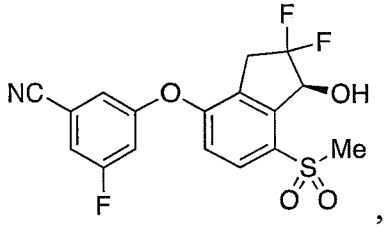
R_5 is hydrogen, halo or alkyl; and

R_8 is hydroxy, alkylamino, alkoxy or amino.

8. The compound of claim 7, wherein R_1 is phenyl or pyridyl, wherein said phenyl or pyridyl is substituted with at least one substituent selected from the group consisting of halo, C1-C4 alkyl, C1-C4 alkoxy, and cyano.

9. The compound of claim 7, wherein R_1 is phenyl, monocyclic heteroaryl, or bicyclic heteroaryl; R_4 is cyano, fluoroalkyl, sulfonamide, sulfinyl, sulfonyl or sulfoximinyl; R_5 is hydrogen; and R_8 is hydroxy or amino.

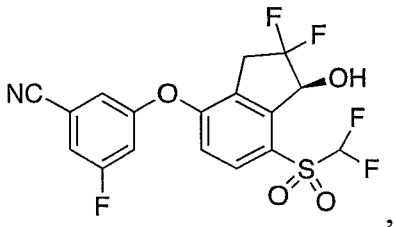
10. The compound of claim 1, wherein the compound is (*S*)-3-((2,2-difluoro-1-hydroxy-7-(methylsulfonyl)-2,3-dihydro-1*H*-inden-4-yl)oxy)-5-fluorobenzonitrile, represented by the formula:



or a pharmaceutically acceptable salt thereof.

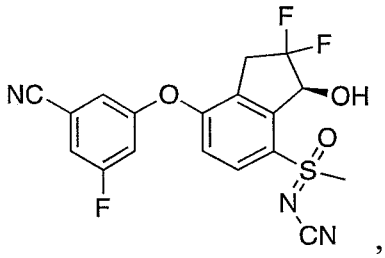
11. The compound of claim 1, wherein the compound is selected from the group consisting of:

(a) 3-[(1*S*)-7-(difluoromethylsulfonyl)-2,2-difluoro-1-hydroxy-indan-4-yl]oxy-5-fluoro-benzonitrile, represented by the formula:



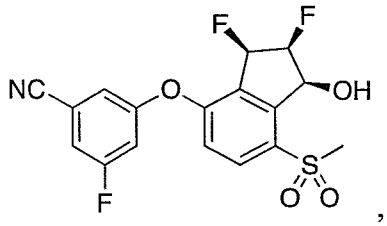
,

(b) *N*-(((*S*)-7-(3-cyano-5-fluorophenoxy)-2,2-difluoro-3-hydroxy-2,3-dihydro-1*H*-inden-4-yl)(methyl)(oxo)-λ^6-sulfanylidene)cyanamide, represented by the formula:



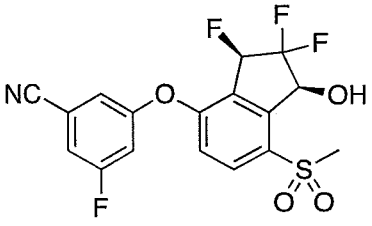
,

(c) 3-[(1*S*,2*S*,3*R*)-2,3-difluoro-1-hydroxy-7-methylsulfonyl-indan-4-yl]oxy-5-fluoro-benzonitrile, represented by the formula:



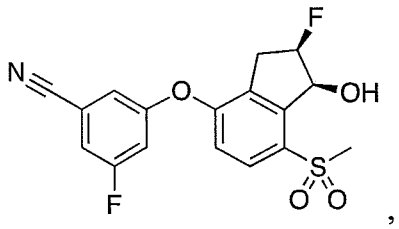
,

(d) 3-fluoro-5-[(1*S*,3*R*)-2,2,3-trifluoro-1-hydroxy-7-methylsulfonyl-indan-4-yl]oxy-benzonitrile, represented by the formula:



, and

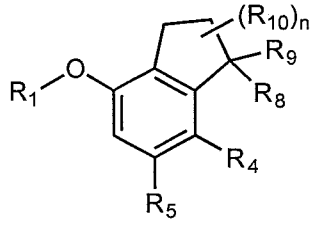
(e) 3-fluoro-5-(((1*S*,2*R*)-2-fluoro-1-hydroxy-7-(methylsulfonyl)-2,3-dihydro-1*H*-inden-4-yl)oxy)benzonitrile, represented by the formula:



or a pharmaceutically acceptable salt of any one thereof.

12. A pharmaceutical composition comprising a compound of claim 1, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

13. Use of a therapeutically effective amount of a compound of Formula III:



III,

or a pharmaceutically acceptable salt thereof, wherein:

n is 1, 2, 3 or 4;

R_1 is aryl or heteroaryl;

R_4 is nitro, halo, cyano, alkyl, sulfinyl, sulfonamide, sulfonyl or sulfoximinyl;

R_5 is hydrogen, halo or alkyl;

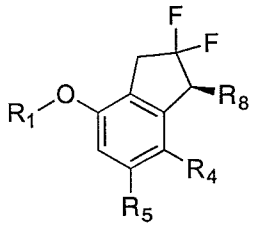
R_8 is hydrogen, hydroxy, alkylamino, alkoxy or amino;

R_9 is hydrogen, alkyl, alkenyl or alkynyl; or R_8 and R_9 in combination form oxo or oxime; and

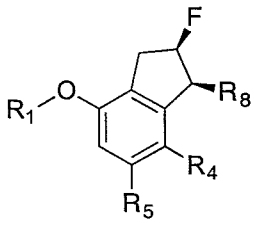
each of R_{10} is independently selected from the group consisting of hydrogen, fluoro, chloro, hydroxy, and alkyl; or two R_{10} and the carbon atom(s) they are attached to form a 3- to 8-membered cycloalkyl or heterocycloalkyl,

in the manufacture of a medicament for treating renal cell carcinoma (RCC) in a subject.

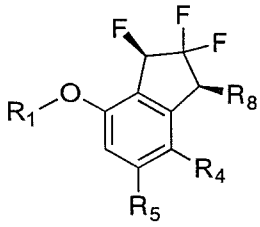
14. The use of claim 13, wherein the compound is represented by Formula Va, Vb, Vc, or Vd:



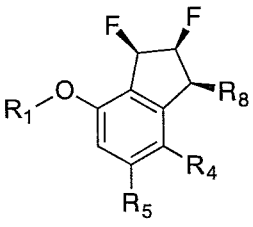
Va



Vb



Vc



Vd

,

or a pharmaceutically acceptable salt thereof, wherein:

R_1 is aryl or heteroaryl;

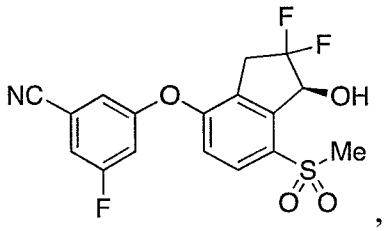
R_4 is halo, cyano, alkyl, sulfonamide, sulfinyl, sulfonyl or sulfoximinyl;

R_5 is hydrogen, halo or alkyl; and

R_8 is hydroxy, alkylamino, alkoxy or amino.

15. The use of claim 14, wherein R_1 is phenyl or pyridyl, wherein said phenyl or pyridyl is substituted with at least one substituent selected from the group consisting of halo, C1-C4 alkyl, C1-C4 alkoxy, and cyano.

16. The use of claim 13, wherein the compound is (*S*)-3-((2,2-difluoro-1-hydroxy-7-(methylsulfonyl)-2,3-dihydro-1*H*-inden-4-yl)oxy)-5-fluorobenzonitrile, represented by the formula:

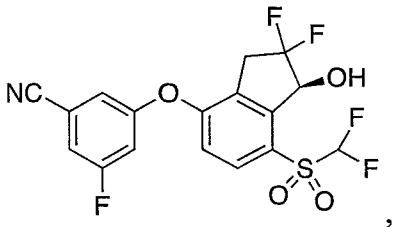


,

or a pharmaceutically acceptable salt thereof.

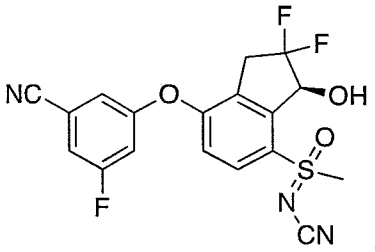
17. The use of claim 13, wherein the compound is selected from the group consisting of:

(a) 3-[(1*S*)-7-(difluoromethylsulfonyl)-2,2-difluoro-1-hydroxy-indan-4-yl]oxy-5-fluoro-benzonitrile, represented by the formula:



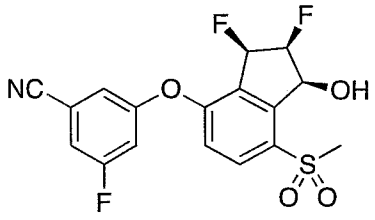
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(b) *N*-(((*S*)-7-(3-cyano-5-fluorophenoxy)-2,2-difluoro-3-hydroxy-2,3-dihydro-1*H*-inden-4-yl)(methyl)(oxo)-λ^6-sulfanylidene)cyanamide, represented by the formula:



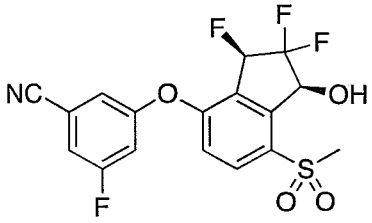
,

(c) 3-[(1*S*,2*S*,3*R*)-2,3-difluoro-1-hydroxy-7-methylsulfonyl-indan-4-yl]oxy-5-fluoro-benzonitrile, represented by the formula:



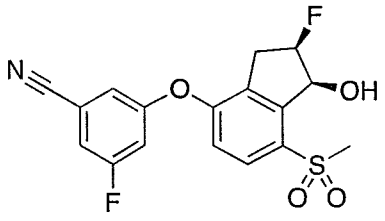
,

(d) 3-fluoro-5-[(1*S*,3*R*)-2,2,3-trifluoro-1-hydroxy-7-methylsulfonyl-indan-4-yl]oxy-benzonitrile, represented by the formula:



, and

(e) 3-fluoro-5-(((1*S*,2*R*)-2-fluoro-1-hydroxy-7-(methylsulfonyl)-2,3-dihydro-1*H*-inden-4-yl)oxy)benzonitrile, represented by the formula:



,

or a pharmaceutically acceptable salt of any one thereof.